Product Information

Lipaglyn™
Saroglitazar

1. COMPOSITION
Each uncoated tablet contains:
Saroglitazar 4 mg
Excipients q.s.
Inactive ingredients in the tablet are microcrystalline cellulose, lactose, magnesium oxide, povidone, talc, magnesium stearate, croscarmellose sodium and colloidal silicon dioxide.

2. DRUG DESCRIPTION
LIPAGLYN™ (Saroglitazar) is a dual regulator that corrects both the lipid profile and the glycemic indices. It is available as an oral tablet containing 4 mg of Saroglitazar. The chemical name for Saroglitazar is Benzenepropanoic acid, \(\alpha\)-ethoxy-4-[2-[2-methyl-5-[4-(methylthio)phenyl]-1H-pyrrol-1-yl]ethoxy]-, magnesium salt (2:1), \((\alpha S)\) - with the following structural formula:

![Structural formula of Saroglitazar](image)

The empirical formula of Saroglitazar is \([C_{25}H_{28}NO_4S]_2\text{Mg}\) and the molecular mass is 900 g/mole.

3. INDICATIONS AND USAGE
LIPAGLYN™ is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by statin therapy. In clinical studies, LIPAGLYN™ has demonstrated reduction of triglycerides (TG), Low Density Lipoprotein (LDL) cholesterol, Very Low Density Lipoprotein (VLDL) cholesterol, non - High Density Lipoprotein (non- HDL) cholesterol and an increase in HDL cholesterol. It has also shown favorable glycemic indices by reducing the fasting plasma glucose and glycosylated hemoglobin in diabetic patients.
4. DOSAGE AND ADMINISTRATION
The recommended dose of LIPAGLYN™ is one tablet of 4 mg once a day.

5. DOSAGE FORMS AND STRENGTHS
LIPAGLYN™ is available as uncoated tablets for oral administration. Each uncoated tablet of LIPAGLYN™ contains 4 mg of Saroglitazar.

6. CONTRAINDICATIONS
Hypersensitivity to Saroglitazar or any of the excipients used in the formulation.

7. WARNINGS AND PRECAUTIONS
Although clinical studies with LIPAGLYN™ have not demonstrated any potential for myopathies or derangement of liver and/or renal function, LIPAGLYN™ treatment should be initiated with caution in patients with abnormal liver or renal function, or history of myopathies. LIPAGLYN™ has not been studied in patients with established New York Heart Association (NYHA) Class III or IV heart failure. LIPAGLYN™ should be initiated with caution in patients with type 2 diabetes having cardiac disease with episodic congestive heart failure and such patients should be monitored for signs and symptoms of congestive heart failure. Although during the clinical studies, no significant weight gain and edema was reported with LIPAGLYN™, patients who experience rapid increase in weight should be assessed for fluid accumulation and volume-related events such as excessive edema and congestive heart failure.

8. ADVERSE EVENTS
In two controlled phase III clinical studies of 12 to 24 weeks treatment duration with LIPAGLYN™, the most common adverse events (AEs ≥ 2%) reported were gastritis, asthenia and pyrexia. Most of the AEs were mild to moderate in nature and did not result in discontinuation of the study. Because clinical studies are conducted under widely varying conditions, AE rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

9. DRUG INTERACTIONS
In vitro studies using recombinant human cytochrome P-450 (CYP) isozymes indicate that Saroglitazar does not significantly inhibit CYP1A2, 2C9, 2C19, 2D6 and 3A4 at concentration of 10μM. Similarly, Saroglitazar did not show
any potential for CYP3A4 enzyme induction when tested up to 100 μM concentration in luciferase based reporter assay in transiently transfected HepG2 cells. Although no clinical drug-drug interaction studies have been conducted with LIPAGLYN™ so far, because the tested concentrations (10 μM and 100 μM) are several times higher than the mean C_max of Saroglitazar, it can be inferred that LIPAGLYN™ would not cause clinically significant drug-drug interactions related to the above evaluated CYPs.

10. USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Pregnancy: Category C

The safety of LIPAGLYN™ in pregnant women has not been established as there is no adequate and well controlled study carried out in pregnant women. Women who become pregnant during LIPAGLYN™ treatment should contact their physicians. LIPAGLYN™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, effects of Saroglitazar on the embryo-fetal development were assessed in pregnant rats given repeated oral doses of 5, 25 and 125mg/kg/day. No maternal or fetal toxicity was noticed at 5 mg/kg, which is about 12-fold higher on body surface area basis than the maximum recommended human dose (MRHD) of LIPAGLYN™ 4 mg. Saroglitazar was found to be non-teratogenic up to the highest dose of 125 mg/kg day in rats.

In pregnant rabbits given repeated oral doses of 10, 50 and 200 mg/kg/day of Saroglitazar, no maternal toxicity was noticed up to 10 mg/kg and no fetal toxicity up to 50 mg/kg. Saroglitazar was found to be non-teratogenic up to the highest dose of 200 mg/kg/day in rabbits.

10.2 Nursing mothers

Nursing mothers should not use LIPAGLYN™ because it is not known whether Saroglitazar is excreted into the breast milk.

10.3 Pediatric use

Safety and efficacy of LIPAGLYN™ in pediatric patients have not been established.

10.4 Geriatric use

Considering the comorbidity and concomitant medications in elderly patients, LIPAGLYN™ should be used with caution in geriatric patients.
11. OVERDOSE
During clinical studies, no incidence of overdose with LIPAGLYN™ has been reported. In case of overdose with LIPAGLYN™, general supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status.

12. CLINICAL PHARMACOLOGY
12.1 Mechanism of action
Saroglitazar is a potent and predominantly Peroxisome Proliferator Activated Receptor (PPAR)-alpha agonist with moderate PPAR-gamma agonistic activity. PPARs are nuclear lipid-activated transcription factors that regulate the expression of various genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes. The pharmacological effects of Saroglitazar were extensively evaluated in various preclinical models. Saroglitazar showed both anti-dyslipidemic and anti-diabetic effects mainly mediated via activation of PPAR\(\alpha\) and PPAR\(\gamma\) respectively.

PPAR\(\alpha\) activation by Saroglitazar increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of TG. This in turn increases diversion of FA from peripheral tissues (e.g. skeletal muscle and fat tissue) to the liver, and thereby decreasing both FA synthesis and delivery of TG to peripheral tissues. Saroglitazar also causes increased lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase (LPL) and reducing production of apolipoprotein C-III (an inhibitor of LPL activity). Consistent with the above mechanism, Saroglitazar was also found to reduce plasma LDL cholesterol. PPAR\(\alpha\) activation by Saroglitazar also induces an increase in the synthesis of apolipoproteins A-I, A-II and HDL-cholesterol. Although Saroglitazar is predominantly a PPAR\(\alpha\) agonist, it also causes activation of PPAR\(\gamma\) and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Saroglitazar increases the expression of numerous PPAR\(\gamma\)-responsive genes involved in carbohydrate and lipid metabolism, including adiponectin, adipocyte fatty-acid-binding protein (aP2), LPL, fatty acid transport protein (FATP) and fatty acid translocase (CD36). By increasing the expression of these genes, Saroglitazar decreases the post prandial rise of plasma free fatty acids, improves post-absorptive insulin-mediated suppression of hepatic glucose output, reduces the metabolic burden on liver & muscle and promotes glucose
utilization. Robust anti-diabetic and insulin sensitizing effects of Saroglitazar were observed in preclinical models, in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues.

12.2 Pharmacodynamics
12.2.1 Dyslipidemia with Type-II Diabetes Mellitus (T2DM):
The effects of LIPAGLYN™ at a dose of 4 mg per day were assessed in two Phase-III randomized, double-blind, parallel-group studies including diabetic patients with Triglycerides >200 mg/dL. In one study, the patients were treated with LIPAGLYN™ 4 mg or Pioglitazone (45 mg) for 24 weeks. The results are presented in Table 1 below:

<table>
<thead>
<tr>
<th>Time point</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-46.1 ±5.6*#</td>
<td>-45.7 ±5.1*#</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-7.3 ±3.6*</td>
<td>-6.9 ±3.8*#</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-0.4 ±6.5</td>
<td>-4.8 ±6.2*</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>-46.1 ±5.6*#</td>
<td>-46.1 ±5.2*#</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>10.0 ±3.7*</td>
<td>4.6 ±3.9</td>
</tr>
<tr>
<td>Apo A1</td>
<td>0.7 ±4.8</td>
<td>2.2 ±8.2</td>
</tr>
<tr>
<td>Apo B</td>
<td>-11.9 ±5.4*</td>
<td>-9.8 ±5.4*</td>
</tr>
<tr>
<td>FPG^</td>
<td>-15.2 ±3.5*</td>
<td>-11.5 ±5.8*</td>
</tr>
<tr>
<td>HbA1c</td>
<td>-0.3 ±0.1*</td>
<td>-0.3 ±0.1*</td>
</tr>
</tbody>
</table>

All values are presented as Least Square Mean (LSM) ± Standard Error (SE) of Per Protocol (PP) population,
*Statistically significant change as compared to the baseline
#Statistically significant change as compared to Pioglitazone,
^ FPG values presented as Mean ± SE of PP population
When compared to Pioglitazone, **LIPAGLYN™** 4 mg achieved the ATP III goal in more subjects as depicted in Table 2.

<table>
<thead>
<tr>
<th>ATP Goal*</th>
<th>LIPAGLYN™ 4 mg (%)</th>
<th>Pioglitazone 45 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not achieved even one criteria</td>
<td>29.4</td>
<td>50.0</td>
</tr>
<tr>
<td>Achieved one criteria</td>
<td>26.5</td>
<td>22.7</td>
</tr>
<tr>
<td>Achieved two criteria</td>
<td>35.3</td>
<td>27.3</td>
</tr>
<tr>
<td>Achieved all three criteria</td>
<td>8.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* ATP – Adult Treatment Panel III of US National Cholesterol Educational Program, 2002-2003,
  Male : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 40 mg/dl,
  Female : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 50 mg/dl
In another study, the effect of LIPAGLYN™ at 4 mg per day was assessed in diabetic patients with hypertriglyceridemia not controlled with Atorvastatin 10 mg therapy. The patients were treated with LIPAGLYN™ 4 mg or placebo for 12 weeks along with Atorvastatin 10 mg. The results are presented in Table 3 below:

Table 3: Percent change in lipid and glycemic parameters following LIPAGLYN™ 4 mg treatment

<table>
<thead>
<tr>
<th>Time point</th>
<th>Week 6</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-46.4 ±3.1*#</td>
<td>-47.2 ±3.2*#</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-23.6 ±1.9*</td>
<td>-25.8 ±1.8*#</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>-28.1 ±2.5*</td>
<td>-30.7 ±2.4*#</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>-45.1 ±3.3*#</td>
<td>-46.5 ±3.2*#</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>8.3 ±2.8</td>
<td>8.1 ±2.5#</td>
</tr>
<tr>
<td>ApoA1</td>
<td>8.1 ±3.2</td>
<td>9.2 ±4.5</td>
</tr>
<tr>
<td>Apo B</td>
<td>-29.1 ±2.4*</td>
<td>-32.1 ±2.3*#</td>
</tr>
<tr>
<td>FPG</td>
<td>-14.9 ±3.7*#</td>
<td>-10.5 ±4.2*#</td>
</tr>
</tbody>
</table>

All values are presented as LSM ± SE of PP population,
*Statistically significant change as compared to the baseline,
#Statistically significant change as compared to the placebo
In combination with Atorvastatin, LIPAGLYN™ achieved the ATP-III goal in more subjects than Atorvastatin alone; hence demonstrating better cardiovascular risk reduction. (Table 4)

<table>
<thead>
<tr>
<th>ATP Goal *</th>
<th>LIPAGLYN™ 4 mg + Atorvastatin 10 mg (%)</th>
<th>Placebo + Atorvastatin 10 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not achieved even one criteria</td>
<td>10.3#</td>
<td>30.1</td>
</tr>
<tr>
<td>Achieved one criteria</td>
<td>30.8</td>
<td>38.6</td>
</tr>
<tr>
<td>Achieved two criteria</td>
<td>43.6</td>
<td>24.1</td>
</tr>
<tr>
<td>Achieved all three criteria</td>
<td>15.4</td>
<td>6.0</td>
</tr>
</tbody>
</table>

* Male : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 40 mg/dl  
Female : Triglyceride < 150 mg/dL, LDL < 100 mg/dL, HDL > 50 mg/dl  
# significantly different from placebo + Atorvastatin 10 mg

LIPAGLYN™ has also shown a decrease in TG, LDL, VLDL, non-HDL cholesterol and TC with an increase in HDL in non-diabetic patients. There was no incidence of hypoglycemia reported during Phase I-III trials in both diabetic and non-diabetic subjects.

12.3 Human Pharmacokinetics
The single dose pharmacokinetics of LIPAGLYN™ was assessed across the dose range of 0.125 to 128 mg.
12.3.1 Absorption
Following oral administration in healthy volunteers, peak plasma levels of Saroglitazar occurred at approximately 1 hour post-dosing in both the genders. Maximum plasma concentration ($C_{\text{max}}$) and area under the curve ($AUC_{0-\infty}$) of Saroglitazar increased proportionally with the administered single doses of 0.125 mg - 128 mg per day. After single oral dose of LIPAGLYN™ 4 mg in healthy volunteers, $C_{\text{max}}$ of 337.1 ± 91.0 ng/ml (Mean ± SD, n=6) was observed. Pooled analysis of male and female healthy volunteers showed no gender effect or food effect on pharmacokinetics of Saroglitazar.

12.3.2 Distribution
The mean apparent oral volume of distribution ($V_{d/F}$) of Saroglitazar following single-dose administration of LIPAGLYN™ 4 mg was 20.14 ± 6.92 L. \textit{In vitro} Saroglitazar is extensively protein bound (~ 96%) in human plasma. The mean plasma half-life of Saroglitazar following single dose administration of LIPAGLYN™ 4 mg is 2.9 ± 0.9 hours. Multiple-dose studies in humans have shown that Saroglitazar does not undergo accumulation on repeat dosing once daily for 10 days.

12.3.3 Metabolism
In healthy volunteers, LIPAGLYN™ 4 mg has an apparent oral clearance, $CL/F$, calculated to be 4.8 ± 0.93 L/hr. \textit{In vitro} studies using pooled human liver microsomes showed that Saroglitazar is metabolically stable. Following LIPAGLYN™ 4 mg administration, Saroglitazar was found to be metabolized into three minor oxidative metabolites. The exposure of the most abundant oxidative metabolite was found to be less than 10% of the exposure of Saroglitazar.

12.3.4 Excretion
In healthy volunteers, Saroglitazar was not excreted in the urine indicating that it has non-renal route of elimination. Preclinical studies have shown that Saroglitazar is predominantly eliminated unchanged by the hepatobiliary route.

13. NON CLINICAL TOXICOLOGY
13.1 Acute and Chronic Toxicity Studies
Various acute and chronic toxicity studies were performed in mice, rats and dogs up to a duration of 12 months. In acute dose studies, the maximum tolerated dose (MTD) in Swiss albino mice was 500 mg/kg, and in Wistar rat it was 1200 mg/
kg. Safety pharmacology studies did not reveal any adverse changes in CNS, CVS, respiratory and gastrointestinal parameters. In repeat dose toxicity studies, Saroglitazar was shown to have an acceptable safety profile at doses several-fold higher than the approved human doses. At high doses, the toxic effects observed were mainly the exaggerated pharmacological effects mediated by PPAR mechanisms.

13.2 Impairment of Fertility
Saroglitazar did not show any adverse effects on mating or fertility in male rats up to 125 mg/kg (more than 250 times the approved human dose on body surface area basis). In female rats no adverse effects on fertility were observed up to 3 mg/kg (7 times the approved human dose on body surface area basis). Saroglitazar altered the estrus cyclicity and litter indices at 15 mg/kg which is 35 times the human recommended dose.

During pre- and post-natal developmental study in rats, Saroglitazar did not show any adverse effects on reproductive performance and lactating indices up to 1 mg/kg which is more than the human therapeutic dose.

13.3 Carcinogenicity
Two-year carcinogenicity study of Saroglitazar was conducted in Wistar rats. No potential carcinogenic concern for humans was identified, which was further confirmed by a mechanistic study in non-human primates employing molecular biomarkers.

13.4 Mutagenicity
Saroglitazar was found to be non-mutagenic and non-genotoxic in a battery of genetic toxicology studies, including the Ames bacterial mutagenicity test, chromosomal aberration assay using the peripheral human blood lymphocytes and the mouse micronucleus assay.

14. HOW SUPPLIED
LIPAGLYN™ is supplied as uncoated round biconvex tablets with “4” written on one side and plain on the other side. Available as 4 mg strength.
LIPAGLYN™ tablets are supplied as 10 tablets in an alu-alu blister. Each blister is packed in a mono-carton.

15. STORAGE AND HANDLING INSTRUCTIONS
Store below 25°C and in dry place. Protect from light. Keep out of reach of children.